

REVIEW



Product of natural evolution (SARS, MERS, and SARS-CoV-2); deadly diseases, from SARS to SARS-CoV-2

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ABSTRACT

SARS-CoV-2, the virus causing COVID-19, is a single-stranded RNA virus belonging to the order Nidovirales, family Coronaviridae, and subfamily Coronavirinae. SARS-CoV-2 entry to cells initiated by the binding of the viral spike protein (S) to its cellular receptor. The roles of S protein in receptor binding and membrane fusion makes it a prominent target for vaccine development. SARS-CoV-2 genome sequence analysis has shown that this virus belongs to the beta-coronavirus genus, which includes Bat SARS-like coronavirus, SARS-CoV and MERS-CoV. A vaccine should induce a balanced immune response to elicit protective immunity. In this review, we compare and contrast these three important CoV diseases and how they inform on vaccine development.

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Introduction

Coronaviruses (CoV) are enveloped, positive-sense, single-stranded RNA viruses of the family Coronaviridae with spikes around its spherical body (corona = crown).^{1–4} CoV is the recognized cause of mild respiratory tract infections in humans.^{5–7} The first two HCoVs, HCoV-229E and HCoV-OC43 have been known since the 1960s.⁸ The viruses are subdivided into four genera on the basis of genotypic and serological characters which are Alpha-, Beta-, Gamma, and Delta-coronavirus,^{9,10} and among them CoVs in the first two genera infect humans.^{11–13} Seven CoVs are known to infect humans, three of them seriously, viz., SARS (severe acute respiratory syndrome, China, 2002), MERS (Middle East respiratory syndrome, Saudi Arabia, 2012), and SARS-CoV-2 (2019–20). Which are beta-coronaviruses (beta-CoVs).¹² The viral fusion protein is critical in enveloped virus entry to cells in that it mediates the membrane fusion reaction.^{14–18} CoV entry into target cells is performed by the spike (S) envelope glycoprotein, which mediates both host cell receptor binding and membrane fusion.^{19,20} The history of major epidemic diseases since 1900 is shown in Table 1. The three main CoV outbreaks and their origin is indicated in Table 2. Important steps that allow CoV entry are shown in Table 3. Taxonomy of the CoV family is presented in Figure 1. Host information and distribution of SARS CoVs in GenBank are presented in Table 4.

This manuscript aims to review SARS, MERS, and SARS-CoV-2 while considering their similarities and differences and possible methods to prevent their infection.

Severe acute respiratory syndrome (SARS)

The contagious and sometimes fatal severe acute respiratory syndrome (SARS) is a respiratory illness which first appeared

in China in 2002, and it spread worldwide, mostly by unsuspecting travelers.^{22–24} SARS-CoV belongs to the Beta-coronavirus family but has a “b” lineage. Other members of this family are *Arteriviridae*, *Mesoniviridae*, and *Roniviridae*.²⁵ It is similar to other coronaviruses in both virion structure and genome organization with a single-stranded, plus-sense RNA.^{26,27} CoVs are single-stranded RNA viruses which belong to the order Nidovirales, family Coronaviridae, and subfamily Coronavirinae,^{28–30} and have been classified into four major groups: α -CoVs, β -CoVs, γ -CoVs, and δ -CoVs with 17 subtypes.³¹ It has been reported, SARS-CoV, like other coronaviruses, is an RNA virus which replicates in the cytoplasm, and the virion envelope contains at least three structural proteins, S, E, and M, embedded in the membrane, and also like other coronaviruses, SARS-CoV encodes several group-specific proteins, termed 3a, 3b, 6, 7a, 7b, 8, and 9.^{32–34} Deletion of the small envelope (E) protein modestly reduces SARS-CoV growth in vitro and in vivo,^{35–37} which may result in an attenuated virus. SARS 8b, known as X5 is predicted to be a soluble protein with 84 amino acids and an estimated size of 9.6 kDa.³⁸ It showed minor homology to the human coronavirus E2glycoprotein precursor.³⁹ SARS-CoV encodes an exceptionally high number of accessory proteins that bear little resemblance to accessory genes of other coronaviruses.^{40–43} Like other coronaviruses, SARS-CoV is an inefficient inducer of IFN- β response in cell culture system⁴⁴ and is sensitive to the antiviral state induced by IFNs.^{45,46} Two functional domains of S protein, S1 and S2 located in the N- and C-terminal regions, respectively, of the S protein are conserved among the coronaviruses.⁴⁷ The S protein in coronaviruses is major antigenic determinants that induce immune response in the hosts.^{48–50} The S protein of transmissible gastroenteritis virus contains four major antigenic sites (A–D), and site A on the S1

Table 1. History of epidemics since 1900.

Year	Outbreak
1918	Great flu pandemic
1976	Legionnaires disease
1993	Hanta virus pulmonary syndrome
1994	Hendra virus infection
1997	H5N1 influenza infection
1999	Nipah virus encephalitis/pneumonitis
2002	Severe acute respiratory syndrome (SARS)
2012	Middle east respiratory syndrome (MERS)
2019	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Table 2. Three main coronavirus outbreaks and their origin.

Coronavirus outbreak	Origin
SARS	Civets (although, the virus originated in bats, and civets consider as intermediary)
MERS	Camels (The virus also came from bats)
SARS-CoV-2	Malayan pangolins (armadillo-like mammals) (the virus also came from bats)

Table 3. Important steps allow the virus entry.^{20.}

- Bind to a target host cell, typically via interactions with cellular receptors.
- Fuse its envelope with a cellular membrane, either at the plasma membrane or through the endocytic pathway.
- Deliver its genetic material inside the cell.

subunit is the main inducer of neutralizing Abs.^{51–53} Ab responses to SARS-CoV can be developed in SARS patients; but, its antigenic determinants remain to be elucidated.⁵⁴ But, in other coronaviruses, deletion of E results in either complete absence of infectious virus or a severe reduction in titer.^{55,56} DeDiego et al.⁵⁷ reported that E protein is responsible in a significant proportion of the inflammasome activation and the associated inflammation elicited by SARS-CoV in the lung parenchyma, and the inflammation may lead to edema accumulation which cause acute respiratory distress syndrome (ARDS). E protein contains several active motifs despite its small size, between 76 and 109 amino acids depending on the

Table 4. Host information and distribution of SARSr-CoVs available in GenBank.^{21.}

Provinces	Bat species
Guangdong	<i>Rhinolophus sinicus</i>
Guangxi	<i>Rhinolophus pearsonii</i> , <i>Rhinolophus sinicus</i>
Guizhou	<i>Rhinolophus rex</i> , <i>Rhinolophus sinicus</i>
Hebei	<i>Rhinolophus ferrumequinum</i>
Henan	<i>Rhinolophus ferrumequinum</i>
Hong Kong	<i>Rhinolophus sinicus</i>
Hubei	<i>Rhinolophus ferrumequinum</i> , <i>Rhinolophus macrotis</i> , <i>Rhinolophus sinicus</i>
Jilin	<i>Rhinolophus ferrumequinum</i>
Shaanxi	<i>Rhinolophus pusillus</i>
Shanxi	<i>Rhinolophus ferrumequinum</i>
Taiwan	<i>Rhinolophus monoceros</i>
Yunnan	<i>Aselliscus stoliczkanus</i> , <i>Rhinolophus affinis</i> , <i>Rhinolophus ferrumequinum</i> , <i>Rhinolophus sinicus</i>
Zhejiang	<i>Rhinolophus monoceros</i> , <i>Rhinolophus pearsonii</i> , <i>Rhinolophus sinicus</i> , <i>Rhinolophus thomasi</i>

Table 5. The most important characteristic of SARS.

- The first international disease epidemic of the twenty-first century.
- It is the first time this Coronavirus has been found in humans.
- It was the first public health challenge for international communities.
- The first disease that globalization visibly exacerbated its spread in a short time and contributed significantly to its end.

CoV.^{58,59} The most important characteristics of SARS are shown in Table 5. Possible origins of SARS-CoV-2 and homologous analysis of SARS-CoV-2 (NC_045512) and six other Coronavirus strains isolated from different hosts in China are shown in Tables 6 and 7, respectively. Most relevant clinical similarities and differences between SARS-CoV and SARS-CoV-2 are presented in Table 8.

SARS should not be confused with avian flu which is another zoonosis from the same area. It initially began in the Guangdong province in south of China in 2002–2003 which eventually involved more than 8400 people worldwide, which is around 9.5% of the total affected.^{63–65} The greatest number of SARS cases were in mainland China, Hong Kong, Taiwan, Singapore, Canada, respectively.^{66–68} Quick infection is one of

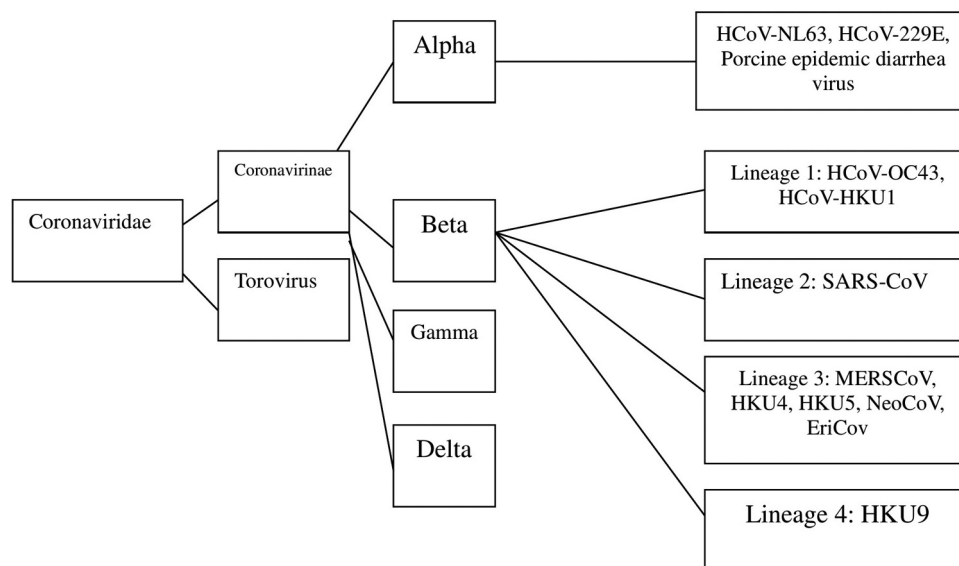
**Figure 1.** Taxonomy of the coronaviridae family.

Table 6. Possible origins of SARS-CoV-2.⁶⁰

- (1) The virus evolved to its current pathogenic state via natural selection in a non-human host and then jumped to humans. Bats are more likely reservoir of SARS-CoV-2 because it is similar to a bat coronavirus, and it may be an intermediate host was involved between bats and humans.
- (2) A nonpathogenic version of the virus transferred from an animal host into humans and then evolved to its current pathogenic state within the human population. Armadillo-like mammals in Asia and Africa, have an RBD structure which is similar to that of SARS-CoV-2. A coronavirus from a pangolin may possibly have been transmitted to a human, directly or through an intermediary host like civets or ferrets.

the main character of SARS.^{69–71} The most important symptoms of SARS were fever, chills, muscle aches, headache, and diarrhea, which may lead to fever with body temperature of 38°C or higher, dry cough and shortness of breath after around one week.^{72–74} On the basis of former reports the features of the clinical examination found in the patients at admission were self-reported fever (99%), documented elevated temperature (85%), nonproductive cough (69%), myalgia (49%), and dyspnea (42%).^{75–78} SARS spread through droplets which enter the air with coughs, sneezes or talks; moreover, it may spread on contaminated objects and surfaces like doorknobs, elevator buttons, and telephones. SARS-CoV is transmitted mainly by person-to-person infection. During its outbreak, nearly 25% of people had severe respiratory failure and 10% died, and it was controlled by using public-health measures, namely, wearing surgical masks, washing hands, and isolating infected patients.^{79–82} Face to face contact of SARS can be divided into three groups, (1) caring for someone with SARS, (2) having contact with the bodily fluids of a person with SARS, and (3) kissing, hugging, touching or sharing eating or drinking utensils with an infected person.^{83–85} Almost 25% of cases developed severe pulmonary disease which may lead to death from respiratory failure.⁸⁶ SARS which had flu-like signs can

lead to death in severe conditions due to respiratory failure or complications consist of heart and liver failure, especially for those old people who had diabetes and hepatitis.^{87–89} Like the common cold, it is caused by a strain of corona CoV. Coronaviruses may lead to severe disease in animals, and it is supposed that the SARS virus might have come from animals to humans.^{90–92} SARS-CoV originated in wild bats and then spread to palm civets or similar mammals. Bats and Civets which are cat-like serve as foods and in folk medicines. Musk production from the scent glands of civets which is used in perfumes is another usage of civets. These mentioned animals could easily transmit the virus to humans.⁹³

Table 9 shows the most important symptoms of SARS and MERS from the highest to the lowest in criticality, while criteria for disease control and prevention case definition of SARS are presented in Table 10. Case classification of SARS is shown in Table 11.

No medication has been proven to treat SARS effectively, but oxygen therapy and tracheal intubation and mechanical ventilation to support life until recovery begins is useful for patients in severe cases.⁹⁵ The most useful ways to control SARS pandemic are public-health and infection-control measures.^{96–105} Peiris¹⁰⁶ confirmed that its rapid mobilization and coordination of relevant expertise when it faced with a global emerging disease threat, which highlighted its needs for improved international regulations governing the reporting of and response to unusual infectious-disease syndromes. Circulating air with high-efficiency particulate air (HEPA) filter to decontaminate, wearing masks and isolating a patient in a single room and wearing a gown, gloves, eye shield, and mask or a portable air purifier which filters out small infectious particles (N95 mask) for staffs are necessary. Hui and Chan¹⁰⁷ found that horseshoe bats are implicated in the emergence of

Table 7. Homologous analysis of SARS-CoV-2 (NC_045512) and six other Coronavirus strains isolated from different hosts in China (%).⁶¹

Isolate	Host	Complete genome	ORF1ab	N	S
SARS coronavirus civet020 (AY572038)	Civet	73.58	79.23	87.79	71.41
Bat SARS-like coronavirus As6526 (KY417142)	Aselliscus stoliczkanus	74.58	79.23	87.55	68.17
Bat SARS-like coronavirus Rs4874 (KY417150)	Rhinolophus sinicus	71.98	79.18	87.94	71.29
Alphacoronavirus Mink/China/1/2016 (MF113046)	Mink	34.97	38.47	33.70	30.89
Bat coronavirus isolate RaTG13 (MN996532)	Rhinolophus affinis	93.7	96.5	96.9	92.86
Pangolin coronavirus (MT084071)	Manis javanica	?	?	95	90

Note: N, N protein. S, spike protein. ?, Sequence of Pangolin coronavirus (MT084071) is not completed in this part of genome.

Table 8. Most relevant clinical similarities and differences between SARS-CoV and SARS-CoV-2.⁶²

Characteristic	SARS-CoV	SARS-CoV-2
Target receptor	ACE-2	ACE-2
N protein	IFN-γ inhibitor	Unknown
R0	0.4	1.4–2.5
Chest X-ray	Ground glass opacities	Bilateral, multilobar ground glass opacities
Chest CT-scan	Lobar consolidation Nodular opacities	No nodular opacities
Prevention	Hand hygiene, cough etiquette	Possibly hand hygiene, cough etiquette
Transmission	Droplets Contact with infected individuals	Droplets even asymptomatic ones
Case fatality rate (overall)	9.6%	2.3%

Abbreviations: SARS-CoV, Severe Acute Respiratory Syndrome Coronavirus; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; N protein, Nucleocapsid protein; IFN-γ, interferon-γ; R₀, R through; X-ray, radiography; CT-scan, computerized tomography.

Table 9. The most important symptoms of SARS and MERS from the highest to the lowest.

SARS	MERS
Fever more than 30°C	Fever
Dry cough	Cough
Sore throat	Shortness of breath
Problems in breathing, such as shortness of breath, inability to maintain oxygenation (hypoxia)	Sore throat
Headache	Diarrhea
Body aches and muscles pain	Head and body aches
Loss of appetite	Vomiting
Malaise	Chest pain/tightness
Night sweats and chills	Running nose
Confusion	Altered conscious/confusion
Rash	Sweating
Nausea, vomiting and diarrhea	Abdominal pain
Weakness	Weakness/fatigue
Fever	Dizziness
Poor appetite	Loss of appetite
Respiratory distress syndrome (ARD or ARDS)	Shivering
Attacking the alveoli (air sacs) in the lungs	
Kidney failure	
Inflammation of the heart sac (pericarditis)	
Sever systematic bleeding from disruption of clotting system (disseminated intravascular coagulation)	
Reduced lymphocyte cell counts (lymphopenia)	
Inflammation of the arteries (vasculitis)	

Table 10. Criteria for disease control and prevention case definition of SARS.⁹⁴

Clinical Criteria	Characteristics
Asymptomatic or mild respiratory illness	
Moderate respiratory illness	Temperature of > 100.4°F (>38° C)
Severe respiratory illness	One or more clinical findings of respiratory illness (e.g. cough, shortness of breath, difficulty breathing, or hypoxia) Temperature of >100.4°F (>38°) One or more clinical findings of respiratory illness (e.g. cough, shortness of breath, difficulty breathing, or hypoxia) Radiographic evidence of pneumonia Respiratory distress syndrome Autopsy findings consistent with pneumonia or respiratory distress syndrome without an identifiable cause
Epidemiologic Criteria	Travel (including transit in an airport) within 10 days onset of symptoms to an area with current or previously documented or suspected community transmission of SARS Close contact within 10 days of onset of symptoms with a person known or suspected to have SARS
Laboratory Criteria	
Confirmed	Detection of antibody to SARS-CoV in specimens obtained during acute illness or >21 days after illness onset Detection of SARS-CoV RNA by RT-PCR confirmed by a second PCR assay, by using a second aliquot of the specimen and a different set of PCR primers Isolation of SARS-CoV
Negative	Absence of antibody to SARS-CoV in convalescent serum obtained >21 days after symptom onset
Undetermined	Laboratory testing either not performed or incomplete

novel coronavirus infection in humans. Ding et al.¹⁰⁸ indicated that in addition to viral spread through a respiratory route, SARS-CoV in the intestinal tract, kidney, and sweat glands

Table 11. Case classification of SARS.

Under investigation	A person who has been referred to the public health service for possible SARS-CoV infection
Suspected case	A person with all of these following: (a) Sudden onset of high fever, > 38°C (b) One or more of the following respiratory symptoms: cough, sore throat, shortness of breath, and difficulty in breathing (c) Showing symptoms within 10 days of either traveling to one of the suspected areas of SARS or being in close contact with a person who has traveled to those areas
Probable case	(a) A suspected case with chest X-ray findings of pneumonia or adult respiratory distress syndrome (b) A person with an unexplained respiratory illness resulting in death, with a postmortem examination demonstrating the pathology or respiratory distress syndrome without an identifiable cause
Confirmed case	A clinically compatible illness which is confirmed by laboratories
Not a case	A case that has been investigated and subsequently found not to meet the case definition

maybe excreted via feces, urine, and sweat, so leading to virus transmission. The three-dimensional structure result indicates that the nsp2 protein of GD strain is high homologous with 3 CL(pro) of SARS-CoV urban strain, 3CL(pro) of transmissible gastroenteritis virus and 3CL(pro) of human coronavirus 229E strain, which further suggests that nsp2 protein of GD strain possesses the activity of 3CL(pro).^{109,110} Rabenau et al.¹¹¹ showed that SARS-CoV can be inactivated easily with commonly used disinfectants. Cao et al.¹¹² showed that SARS transmission changes in its epidemiological characteristics and SARS outbreak distributions show palpable clusters on both spatial and temporal scales, also its transmission features are affected by spatial heterogeneity. Lessons learned from the SARS outbreak and concerns identified by WHO because of SARS are presented in Table 12. Duration of clinical phases of the mild and moderately severe variants of severe acute respiratory syndrome is shown in Table 13.

The Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

The middle East respiratory syndrome coronavirus (MERS-CoV) is a zoonotic beta coronavirus which can infect various kinds of animals such as humans, camels, and bats.^{118–123} It belongs to the Beta-coronavirus genus, of the coronavirus family.^{124,125} It was first discovered in September 2012 as the cause of death in a patients who had died of severe pneumonia in June 2012 in Jeddah, Saudi Arabia,^{126,127} and 1,348 cases of MERS-CoV infection confirmed globally, with at least 479 related deaths until June 23, 2015.¹²⁸ It has exported from the Middle East to other countries even countries in Asia, Europe, and North America.^{128–133} The most important characteristics of MERS-CoV infections are shown in Table 14.

Routine measures for travelers to help preventing the spread of viruses are hand washing, personal hygiene, avoid contacts with sick people, and animals, and covering the mouth with a tissue when coughing or sneezing and dispose properly the used tissue.¹³⁷ MERS-CoV is most likely derived from an ancestral reservoir bats.^{143–146} Except for some cases in Korea in 2015, 82% of infections have occurred in Saudi Arabia, and

Table 12. Lessons learned from the SARS outbreak and concerns identified by WHO because of SARS.^{113–116.}

Lesson	Means	Concerns
The capacity of global alerts to improve awareness and vigilance	Wide support by responsible press and amplified by electronic communications	Inadequate surge capacity in hospitals and public health systems
The advantage of quick detection and reporting	Immediate reporting of initial cases by South Africa and India	Healthcare providers themselves being the victims of the disease
The successful containment that can be achieved by readying health services with preparedness plans and campaigns to guard against imported cases	Climate of high alert that was established after reports of the disease became known	Shortage of expert staff to coordinate national and global responses to a rapidly evolving public health emergency
The value of immediate political commitment at the highest level	The experience in Vietnam, where the government took immediate measures to protect its people	In some cases, the need for hasty construction of new facilities; in other cases, hospitals being closed
The ability of even developing countries to triumph over a disease when reporting is prompt and open and when rapid case detection, immediate isolation and infection control, and vigorous contact tracing are put in place	The appeal by Vietnam, where WHO assistance was requested quickly and fully supported	The power of poorly understood infectious diseases to incite widespread public anxiety and fear, social unease, economic losses, and unwarranted discrimination

Table 13. Duration of clinical phases of the mild and moderately severe variants of severe acute respiratory syndrome^{112.}

Time	Phase Respiratory			
	Prodrome	Early	Late	Recovery
From onset, days	0	2–7	8–12	14–18
Duration, days	2–7	1–10	5–10	5–7

Table 14. The most important characteristics of MERS-CoV infections.

- (1) MERS-CoV infects more males than females^{134–136}
- (2) It is accompanied by a cluster of flu-like symptoms^{137–139}
- (3) Life threatening severe illnesses consist of acute respiratory distress syndrome, pneumonia, myocarditis, and organ failure^{135,136,140–142}
- (4) Death occurs in 30% to 60% of the cases¹³⁵
- (5) Those who have preexisting medical conditions such as diabetes, cardiovascular diseases, renal failure, obesity, and immunodeficiency are more vulnerable to this disease^{135,137}

the human mortality rate of MERS-CoV infection was nearly 35%.^{147–149} It has been reported that patients with severe diseases have at least one underlying condition, including diabetes, hypertension, chronic cardiac disease, and chronic renal disease.^{150,151} Human to human transmission has been facilitated in healthcare settings^{152,153} with the contribution of hospital-based transmission of MERS estimated at about 80% using an epidemic model.¹⁵⁴ MERS outbreak was found in the Republic of Korea since 2015,¹⁵⁵ which showed the importance risk of importing MERS and escalate global spread of MERS and damage to both economic and public health activities,^{156,157} which show the importance of travel restrictions for infected countries.^{158,159} The key receptor for MERS-CoV infection which is dipeptidyl peptidase 4 (DPP4), is widely distributed on human endothelial and epithelial cells.¹⁴⁷ CoV entry is initiated by the binding of the spike protein (S) to cell receptors, specifically, DPP4 and angiotensin converting enzyme 2 (ACE2) for MERS-CoV and SARS-CoV, respectively. Its genome is a single-stranded RNA which encodes 10 proteins including two replicase polypeptides (open reading frames [ORF], 1 ab and 1 a), three structural proteins (E, N, and M), a surface glycoprotein (S, spike) which comprises S1 and S2, and five nonstructural proteins (ORF 3, 4a, 4b, and 5).^{160–162} The subunit S1 is composed of four different core domain,¹⁶³ and the domain S1B binds to the host-cell receptor

dipeptidylpeptidase 4 (DPP4),^{162,164,165} while the domain S1A binds to sialoglycans which increased infection of human lung cells by MERS-CoV.¹⁶⁶ It has been concluded that the MERS-S protein is known to represent a key target for the development of new therapeutics and includes of a receptor-binding subunit S1 and a membrane-fusion subunit S2.¹⁶⁷ The roles of S protein in receptor binding and membrane fusion make it a perfect target for vaccine and antiviral development.¹⁶⁸ It has been shown that vaccines based on the S protein can induce antibodies to block virus binding and fusion or neutralize virus infection.^{169–171} The subunit S2 includes the fusion peptide, two heptad repeats and a transmembrane domain, which mediate fusion of the virus with the cell membrane.^{172,173} Antibodies against MERS-CoV have been found among both dromedary camel populations and camel-exposed humans, which have been recognized as the source of multiple MERS case importations around the world.^{174,175} Previous studies have investigated viral vector-based vaccines,^{176–180} subunit vaccines,^{181–183} and DNA vaccines,^{184–188} but there is no clinically approved vaccine for MERS-CoV. Among these vaccines, viral vectors or DNA immunization successfully generated neutralizing antibodies and protected against infection.

The 5'/end of the genome contains the rep1a and rep1b genes, which encode the viral replicase-transcriptase. At the 3'/end of genome, four structural protein, namely spike (S), envelope (E), membrane (M), and nucleocapsid (N) protein and five accessory proteins (ORF3, ORF4a, ORF4b, ORF5 and ORF8) make up 10 kb.^{189–191} Kasem et al.¹⁹² and Dighe et al.¹⁹³ showed that camels are a main reservoir for the maintenance of MERS-CoVs, and they are an important source of human infection with MERS. Al-Tawfiq et al.¹⁹⁴ found that MERS-CoV was a rare cause of community acquired pneumonia and other viral causes such as influenza which are more common. Alfaraj et al.¹⁹⁵ found that different factors contributed to increase mortality rate for MERS-CoV patients, and one of the most important factor is usage of corticosteroid and a continuous renal replacement therapy (CRRT). Corman et al.¹⁹⁶ found that the kit is important tool for assisting in the rapid diagnosis, patient management, and epidemiology of suspected MERS-CoV cases. Yoon et al.¹⁹⁷ found that 6,8-difluoro-3-isobutyryl-2-((2,3,4-trifluorophenyl)amino)quinolin-4(1 H)-one (6 u) shows high inhibitory influence and

low toxicity activities which is from 3-Acyl-2-phenylamino-1,4-dihydroquinolin-4(1 H)-one derivatives. Qiu et al.¹⁹⁸ indicated that hMS-1 might be developed as an effective immunotherapeutic agent to cure patients infected with MERS-CoV, especially in emergent cases. Early MERS-CoV diagnosis may require more sensitive risk assessment tools to reduce avoidable delays, specifically those related to patients and health system.^{199–204} Alqahtani et al.²⁰⁵ noted that still many people have lack of accurate understanding about MERS-CoV transmission and prevention, and more studies need to examine the knowledge and practices among public and workers about MERS-CoV.^{206–209} Close contacts include airplane setting, household setting, household setting who also visited the patient in hospital, healthcare setting.^{210,211} Al-Tawfiq and Auwaerter²¹² suggested proper infection control procedures, prompt recognition, isolation and management of suspected cases are important parameters for MERS prevention. Kim²¹³ mentioned the importance of protecting healthcare providers from severe both physical and psychological stress. Al-Tawfiq et al.²¹⁴ reported notable increase in costs of the healthcare system because of increase in utilization of surgical masks, respirators, soap, and alcohol-based hand sanitizers Douglas et al.²¹⁵ indicated that the extent of MERS-CoV adaptation determines the minimal infectious dose needed to achieve severe respiratory disease. Nikiforuk et al.²¹⁶ reported that viral infectious clone system may shorten time between emergence of a novel viral pathogen and construction of an infectious clone system. Ebihara et al.²¹⁷ found that virus infectious clone systems allow for expression of a homogenous virus population within mammalian cell culture from a sequence of DNA or RNA. Letko et al.²¹⁸ demonstrated that MERS-CoV spike can utilize multiple paths to rapidly adapt to novel species variation in DPP4. Zhang et al.²¹⁹ found that MERS-4 neutralizes MERS-CoV by indirect rather than direct competition with DPP4. MERS-CoV nanoparticle vaccine produced high titer anti-S neutralizing antibody and protected mice from MERS-CoV infection in vivo. Mustafa et al.²²⁰ suggested application of antimicrobial peptides (AMPs) as alternative

therapeutic agents against MERS-CoV infection. Baharoon and Memish²²¹ emphasized on balance in application of both vaccination and antiviral therapeutics, also they highlighted the importance of avoid mechanism of escape mutant virus strains and improve activity against divergent virus strains. Widagdo et al.²²² reported vaccination of dromedary camels is an appropriate way to decrease human MERS cases. Comparison between SARS and MERS-CoV in respect to their virology, epidemiology and clinical outcomes are shown in Table 15. The differences between MERS-CoV and SARS-CoV in symptoms, signs, laboratory tests, and chest film are indicated in Table 16.

Enhanced infection control measures which are effective in controlling nosocomial outbreaks and Middle East Respiratory Syndrome CoVs are shown in Tables 17 and 18, respectively.

SARS-CoV-2 coronavirus

The novel SARS-CoV-2 coronavirus which apparently first infected humans in Wuhan China, has caused the COVID-19 pandemic.^{237–239} It is called SARS-CoV-2 because of its high similarity in terms of clinical symptoms and biological nature with the causative agent of severe acute respiratory syndrome (SARS) by the International Committee on Taxonomy of Viruses,^{240,241} which can affect patients of all ages.^{242,243} Its genome sequence analysis has shown that SARS-CoV-2 belongs to beta-coronavirus genus, which includes bat SARS-like coronavirus SARS-CoV and MERS-CoV.²⁴⁴ Its outbreak in China since December 2019 has caused so many challenges, and it has rapidly spread to many countries.^{245–248} It belongs to a large family of viruses which are known as coronaviruses.²⁴⁹ It emerged after 2003 SARS in China and the second coronavirus, which was famous as MERS in 2012 in Saudi Arabia. On the basis of nucleic acid sequence similarity, the newly identified SARS-CoV-2 is a beta-coronavirus.^{250,251} It is mainly associated with respiratory disease and few extrapulmonary signs.²⁵² Epidemiological investigations showed that different animals (Bbats, pangolins, snakes) could have been

Table 15. Comparison between SARS and MERS-CoV in respect to their virology, epidemiology, and clinical outcomes.^{224.}

	MERS-CoV	SARS
Virology	<i>Betacoronavirus</i> lineage 2 C	<i>Betacoronavirus</i> lineage 2B
Receptor	hDPP4	ACE2
Genome size	29.9 kb	29.3kb
Source	Not yet confirmed, camel is the likely host	Civet Cat
Epidemiology	Limited human to human transmission, the disease is mostly localized in the Middle East	Human to human transmission is well-recognized, affected many countries but spared the Middle East
R ₀	2–3 (for Jeddah 3.5–6.7, for Riyadh 2–2.8)	Variable, ranges from 2 to 6
Superspreading event	Not known	Reported
M:F	1.74:1	0.75:1
Median age (range) in years	48 (1–99)	Less than a third had
Mean incubation period in days (range)	5 (2–15)	Comorbidities
Comorbidities	Three quarter of the patients had comorbidities	Less than a third has Comorbidities
Clinical presentation	Unpredictable and erratic clinical course ranging from asymptomatic illness to severe pneumonia	A typical biphasic clinical course
Hemoptysis	More common	Less common
Respiratory failure	Presents relatively early	Presents relatively late
Travel association	Limited travel-associated exposure	Recognized travel-associated exposure
Time from symptom onset to hospitalization	0–16 days	2–8 days
Median time from symptom onset to death	12 days	21 days

Table 16. The difference between MERS-CoV and SARS-CoV in symptoms, signs, laboratory tests, and chest film.²²⁵

Symptoms	MERS-CoV	SARS-CoV
Headache	++	++
Fever and chills	+++	+
Prominent fatigue	+	-
Myalgias	++	+++
Dry cough	+++	++
Shortness of breath	+++	++
Sore throat	+	+
Nausea/vomiting	+	+
Diarrhea	±	±
Abdominal pain	±	-
Hemoptysis	±	-
Signs		
Tachycardia	+	+
Conjunctival suffusion	+	-
Diminished breath sounds	+	+
Acute renal failure (ARF)	±	-
Laboratory tests		
Normal WBC count	-	-
Leukopenia	+	-
Relative lymphopenia	+++	+++
Thrombocytopenia	++	+++
Elevated serum transaminases	+	±
Elevated ldh	+	++
Elevated cpk	++	-
Chest film		
Normal/minimal basilar infiltrates (early)	-	+
Unilateral infiltrates (late)	+	-
Pleural effusion	+++	++
Cavitation	+	-
ARDS (severe cases)	-	-

Table 17. Enhanced infection control measures that were effective in controlling nosocomial outbreaks.^{226–235}

- (1) Hand hygiene, and droplet and contact precautions for febrile patients with a fever before testing these patients for MERS-CoV.
- (2) Putting surgical masks on all patients undergoing haemodialysis, and ensuring health-care workers wear N95 filtering facepiece respirators when managing any patient with a confirmed MERS-CoV infection who is undergoing an aerosol-generating procedure.
- (3) Patients with suspected MERS-CoV infection admitted to dialysis or intensive care units should be placed in isolation rooms with a portable dialysis machine.
- (4) Increasing environmental cleaning, and preventing non-essential staff and visitors from coming into contact with patients infected with MERS-CoV.

intermediate hosts which facilitate the spill-over of SARS-CoV-2 as a distinct human Beta-coronavirus from bats to human population.^{253–257} Sun et al.²⁵⁸ reported that bats are considered as the natural hosts of this virus, cold temperature and low humidity provides conducive environmental conditions for prolonged viral survival in suspected regions concentrated with bats. The RBD portion of the SARS-CoV-2 S protein has evolved to effectively target a molecular feature on the outside of human cells called ACE2, a receptor involved in regulating blood pressure.

The SARS-CoV-2 S protein was found so effective at binding the human cells. The SARS-CoV-2 backbone differed substantially from those of known coronaviruses and mostly resembled related viruses found in bats and pangolins. With considering tabular comparison of SARS versus SARS-CoV-2, clinical presentation of SARS and SARS-CoV-2 are fever, dry cough, and shortness of breath; incubation period for SARS and SARS-CoV-2 are 2–7 days, 2–14 days, respectively.²⁵⁹ Its cycle starts when S protein binds to the cellular receptor ACE2;

after receptor binding the conformation change in the S protein facilitates viral envelope fusion with the cell membrane through the endosomal pathway, and then SARS-CoV-2 releases RNA into the host cell. Genome RNA is translated into viral replicase polyproteins pp1a and 1ab, which are then cleaved into small products by viral proteinases. The polymerase produces a series of subgenomic mRNAs by discontinuous transcription and finally translated into relevant viral proteins. Both viral proteins and genome RNA are subsequently assembled into virions in the endoplasmic reticulum (ER) and Golgi, and then transported via vesicles and released out or the cell.²⁶⁰ Kang et al.²⁶¹ reported that the cause and consequence of pneumonia still remain unknown. Previous coronavirus outbreaks have started, with humans contracting the virus after direct exposure to civets (SARS), and camels (MERS).⁶⁰ Tseng et al.²⁶² found that SARS-CoV vaccines all induced antibody and protection against infection with SARS-CoV. Most CoVs share a similar viral structure, similar infection pathway and a similar structure of the S protein,²⁶³ which has shown similar research strategies should be used for SARS-CoV-2.^{264,265} Matsuyama et al.²⁶⁶ discovered that SARS and MERS and SARS-CoV-2 infection is enhanced by TMPRSS2. Rasmussen et al.²⁶⁷ reported an incubation period of ~5 days (range-2–14 days), average age of hospitalized patients has been 49–56 years, with a third to half with an underlying illness, and men were more frequent among hospitalized cases (54–73%). Chan et al.²⁶⁸ reported person-to-person transmission of 2019 novel coronavirus in hospital and family settings, and the reports of infected travelers in other geographical regions. Khan et al.²⁶⁹ reported that during control the SARS-CoV-2, the entrances of residential communities, dormitories, and public places were restricted and temperature monitoring for related symptoms was done before residents entering.^{269–273}

Chen et al.²⁴⁹ showed that on the basis of molecular modeling, SARS-CoV-2 RBD has a stronger interaction with angiotensin converting enzyme 2 (ACE2), and a unique phenylalanine F486 in the flexible loop plays an important role due to its penetration into a deep hydrophobic pocket in ACE2, and ACE2 can potentially bind RBD of SARS-CoV-2, making them all possible natural hosts for the virus. It might be able to bind to the angiotensin-converting enzyme2 receptor in humans.²⁷⁴ Luan et al.²⁷⁵ observed that N82 in ACE2 indicated a closer contact with SARS-CoV-2 S protein than M82 in human ACE2. RBD domain of SARS-CoV-2 interacts with human ACE2, which is why ACE2 is considered as the receptor for SARS-CoV-2.^{275,276} Wall et al.²⁷⁶ showed the presence of a four amino acid residue insertion at the boundary between the S1 and S2 subunits in SARS-CoV-2 S compared with SARS-CoV and SARS-CoV S. Wall et al.²⁷⁶ demonstrated that SARS-CoV s murine polyclonal antibodies potently inhibited SARS-CoV-2 S mediated entry into cells which showed cross-neutralizing antibodies targeting conserved S epitopes can be elicited upon vaccination. Measures to prevent transmission are highly successful at an early stage, and in the next steps on the SARS-CoV-2 infection should be focused on early isolation of patients and quarantine.^{277,278} Possible origins of SARS-CoV-2 are shown in Table 25. In

Table 18 Middle East respiratory syndrome coronavirus vaccines²³⁶.

Vaccine	Target	Use	Advantages	Problems
Anti-MERS-CoV monoclonal antibodies	Surface (S) glycoprotein	Passive immunization; prophylaxis or treatment at early times p.i.	High titer preparations; can be produced in large amounts	Short half-life; needs to be readministered for continued efficacy
Human polyclonal anti-MERS-CoV antibodies	Virus structural proteins	Passive immunization; treatment at early times p.i.	Polyclonal antibody so antibody escape unlikely; human antibody	Short half-life; needs to be readministered for continued efficacy; few MERS survivors available as donors
Inactivated virion vaccines	Virus structural proteins; anti-S neutralizing antibodies most important	Active immunization	High titer antibody to S protein	Response may not be long term; on challenge may induce immunopathological disease; may be ineffective in aged populations
Live attenuated vaccines (e.g. viruses deleted in envelope (E) protein; viruses with reduced fidelity (mutated in nsp14)	Mostly virus structural proteins	Active immunization	Generally safe; induce antibody and T-cell responses; long-term immunity	May not be safe in immunocompromised patients; may regain virulence by reversion or recombination with circulating CoV
Viral vector (attenuated) vaccines: poxvirus, AAV adenovirus, parainfluenza virus, rabies virus, measles virus, VSV	S protein	Active immunization	Safe; nonreplicating; induce antibody and T-cell responses	Long-term immunity, but not as long as live attenuated vaccines
Replicon particles (e.g. VEEV or VSV-based)	S protein or any viral protein	Active immunization	Safe; nonreplicating; induce antibody and T-cell responses; useful for mucosal immunity	Production is complex
Subunit vaccines (e.g. RBD of S protein)	Generally S protein	Active immunization	Safe; non-replicating; induce high antibody titers; may also induce T-cell responses	Duration of response not known
DNA vaccines	Generally S protein	Active immunization	Safe; induce high antibody titers and T-cell responses	Immunogenicity variable; may induce anti-DNA immune response

Abbreviations: MERS-CoV, Middle East respiratory syndrome coronavirus; p.i., post infection; AAV, adeno-associated virus; VSV, vesicular stomatitis virus; VEEV, Venezuelan equine encephalitis virus; RBD, receptor binding domain.

SARS-CoV-2, M protein is responsible for the transmembrane transport of nutrient, the bud release and the formation of envelope, S protein, attaching to host receptor ACE2, including two subunits S1 and S2; S1 determines the virus host range and cellular tropism by RBD, and S2 mediates virus-cell membrane fusion by HR1 and HR2. N, E protein, and several accessory proteins, interfered with host immune response or unknown function. Li et al.⁶¹ reported that genome and ORF1a homology show that the virus is not the same CoV as the CoV derived from five wild animals, namely *Paguma larvata*, *Paradoxurus hermaphrodites*, *Civet*, *Aselliscus stoliczkanus*, and *Rhinolophus sinicus*, whereas the virus has the highest homology with Bat Coronavirus isolate RaTG13. Populations influenced by SARS-CoV-2 divided into four levels is shown in Table 19.

Real-time reverse-transcriptase-polymerase chain reaction (rRT-PCR) may produce initial false negative results, and they have suggested that patients with typical computed tomography (CT) findings, but negative rRT-PCR results should be isolated, and rRT-PCR should be repeated to avoid misdiagnosis.^{280,281}

Table 19. Populations influenced by SARS-CoV-2 divided into 4 levels.²⁷⁹.

- (1) Patients with severe symptoms of SARS-CoV-2, front-line medical staff, researchers or administrative staff.
- (2) Patients with mild symptoms of SARS-CoV-2, close contacts, suspected patients or patients with fever who come to hospital for treatment.
- (3) People related to the first and second-level population, such as family members, colleagues or friends; rescuers, such as commanders, administrative staff, or volunteers.
- (4) People in affected areas, susceptible groups or general public.

Other scientists also stated that final diagnosis relies on rRT-PCR positively for the presence of coronavirus.^{282–284} However, there are currently no effective specific antivirals or drugs combinations supported by high-level evidence.²⁸⁵ Wang et al.²⁸⁶ introduced spiral chest computed tomography (CT) as a sensitive examination method, which can be applied to make early diagnosis and for evaluation of progression with a diagnostic sensitivity and accuracy better than that of nucleic acid detection. Liu et al.²⁸⁷ indicated that on the resolution phase of the disease, CT abnormalities showed complete resolution or demonstrated residual linear opacities. Prem et al.²⁸⁸ noticed that restrictions on activities in Wuhan, would help to delay the epidemic peak and prevent the secondary peak. Sun et al.²⁸⁹ highlighted the importance and availability of public datasets to encourage analytical efforts and provide robust evidence to guide interventions. Kobayashi et al.²⁹⁰ found that the risk of death among young adults is higher than that of seasonal influenza, and those elderly with underlying comorbidities need additional care. Grubaugh et al.²⁹¹ found that many more mutations will appear in the viral genome which these mutations may help scientists to track the spread of SARS-CoV-2. Coronaviruses have capacity to jump species boundaries and adapt to new hosts.²⁹² Zhao et al.²⁹³ reported that the majority of patients with suspected or confirmed SARS-CoV-2 showed fever and dry cough and presented bilateral multiple mottling and ground-glass opacity on chest computed tomography scans. Lippi et al.²⁹⁴ showed that low platelet count is associated with increased risk of severe disease and mortality in patients with SARS-CoV-2, and it can be considered as clinical indicator of worsening illness during hospitalization. Lv et al.²⁹⁵ emphasized

at the importance of successive sampling and testing SARS-CoV-2 by RT-PCR. Xie et al.²⁹⁶ recommended combining the computed tomography scans and nucleic acid detection. Guo et al.²⁹⁷ indicated the strong influence of SARS-CoV-2 epidemic on the utilization or emergency dental services. It has been reported that remdesivir only and in combination with chloroquine or interferon beta significantly blocked the SARS-CoV-2 replication and patients were declared as clinically recovered.^{298–300} Some other anti-virals like Nafamostat, Nitazoxanide, Ribavirin, Penciclovir, Favipiravir, Ritonavir, AAK1, Baricitinib, and Arbidol showed moderate results when tested against infection in patients and in-vitro clinical isolates.³⁰¹ Shen et al.³⁰² consider isothermal nucleic acid amplification as a highly promising candidate method for detection of coronavirus infection, due to its fundamental advantage in quick procedure time at constant temperature without thermocycler operation. Seah and Agrawal³⁰³ found that the ability of SARS-CoV-2 to infect ocular tissue and its pathogenic mechanisms. Ghinai et al.³⁰⁴ classified SARS-CoV-2 into four categories: high-risk contacts, medium-high-risk contact, medium-risk contacts, low-risk contacts and no-contacts. The most important Diagnostic Criteria for SARS-CoV-2 are shown in Table 20.

Human Coronaviruses and Vaccines

No licensed MERS coronavirus vaccine is currently available and the most challenges for progress to have vaccines are (a) available animal models which might not mimic human diseases,³⁰⁷ (b) an immune correlate or protection has not been identified and the protective immune response in natural infection is poorly understood,³⁰⁸ (c) there is a theoretical risk of immune enhancement during MERS coronavirus infection after vaccination possibly leading to immunopathological pulmonary eosinophilic infiltration,³⁰⁹ (d) demonstration of efficacy in the field will probably not be possible, necessitating alternative regulatory pathways for licensure, (e) if MERS shifts from a pattern of sporadic outbreaks to pandemic spread, it is not known whether vaccines based on current MERS coronavirus isolates will offer protection against pandemic strains. Previous work with a double inactivated SARS-CoV had shown efficacy in young mice,³¹⁰ but, subsequent analysis in aged animals or with

heterologous challenge showed vaccine failure and significant immune pathology.³¹¹ Not tested in experimental systems, based on reported cases, age and immune-compromised status appears to be comorbidity factors for MERS-CoV infection and lethality.^{312,313} Spike (S) protein of MERS-CoV is immunogenic and can induce neutralizing antibodies, which is a potential major target for vaccine development.³¹⁴ It is important to prepare for large scale-manufacture of the vaccine antigen.³¹⁵ In viral vaccine design, it is essential to identify the most stable and neutralizing viral receptor binding domain (RBD) fragment, while eliminating unnecessary and non-neutralizing structures as a means of immunofocusing.³¹⁶ Subcutaneous vaccination of a recombinant protein containing RBD of MERS-CoV S fused with Fc of human (RBD-Fc) induced strong systemic neutralizing antibody responses in vaccinated mice.³¹⁷ Spherical virus-like particles (sVLP) display the RBD of MERS-CoV are promising prophylactic candidate against MERS-CoV in a potential outbreak situation.³¹⁸ Potent induction of T-cell responses by single-cycle vectors, indicate that these vectors are excellent alternatives to live-attenuated vesicular stomatitis virus (VSV).³¹⁹ SARS M DNA vaccines which induce human neutralizing antibodies and human monoclonal antibodies against SARS CoV are not developed.³¹⁹ SARS-CoV S DNA vaccine can generate antigen-specific humoral and cellular immune responses which may contribute to long-term protection.³²⁰ Caution should be taken in using inactivated SARS-CoV as a vaccine since it may also cause harmful immune or inflammatory responses.³²¹ Both S-containing ecosomes and the adenoviral vector vaccine induced neutralizing antibody titers.^{322,323} Polypeptides originating from N or S might be a potential target for the generation of a recombinant SARS vaccine.^{324,325} After study of a DNA SARS-vaccine, it has been found that a combination of the vaccine-induced T-helper type 1 (Th1) immune response while the whole killed virus vaccine included T helper type 2 (Th2).³²⁶ A similar approach to a CTL vaccine design may be possible for the SARS-CoV-2 which contain multiple class I epitopes with predicted HLA restrictions consistent with broad population coverage.³²⁷ Better understanding of the pathogenesis of the infection with the covid-19 which in selected cases may lead to a similar clinical picture of macrophage activating syndrome with its associated cytokine storm may bring to an improved diagnostic measurements (Shoenfeld, 2020). Immunoreactive spike-1 proteins from SARS-CoV-2 are expressed on the surface of irradiated target I-cells, so utilizing this innovative strategy, these viral antigen-displaying decoy cells will be developed as a vaccine to protect against SARS-CoV-2 disease (Ji et al., 2020). Overview of vaccine production platforms and technologies for SARS-CoV-2 is shown in Table 21.

Vaccine efficacy is measured by the ability of the antigen to raise a protective immunologic response from V and T cells after exposure to the viral agent. Vaccines can be produced by inactivation of the virus by using an attenuated or weak form of the virus or by using recombinant forms of viral components. Inactivated virus vaccines are relatively safe because they can not revert back to the live form; moreover, they are stable and may not even require refrigeration. Inactivated vaccines may usually require several doses, and some are weakly effective at stimulating an immune response.

Table 20. The most important Diagnostic Criteria for SARS-CoV-2.^{305,306.}

- (1) Supportive epidemiological history.
- (2) Clinical manifestation: Fever; normal or low levels of white blood cells or decreased lymphocyte counts at onset. Chest radiology at early stage is characteristic of multiple small patchy shadows and interstitial changes, more prominent in the extra pulmonary bands. Multiple ground-glass opacities and infiltrations may develop bilaterally with disease progression, with possible consolidation in severe cases.
- (3) Diagnosis: SARS-CoV-2 nucleic acid positive in samples of sputum, pharynx swabs, and secretions of lower respiratory tract tested by real-time reverse-transcriptase-polymerase-chain reaction (rRT-PCR) assay.
- (4) For patients with acute fever ($>37.5^{\circ}\text{C}$ within 72 hours) and normal chest imaging, if the absolute count of peripheral lymphocytes is less than $0.8 \times 10^9/\text{L}$, or the count of CD4^{+} and CD8^{+} T cells decrease significantly, isolation and close observation should be conducted at home even if the first SARS-CoV-2 nucleic acid test is negative. Repeat of rRT-PCR should be considered after 24 h, and a chest CT scan should be performed when necessary.

Table 21. Overview of vaccine production platforms and technologies for SARS-CoV-2³²⁸.

Platform	Target	Existing, Licensed Human Vaccines Using the Same Platform	Advantages	Disadvantages
RNA vaccines	S protein	No	No infectious virus needs to be handled, vaccines are typically immunogenic, rapid production possible.	Safety issues with reactogenicity have been reported.
DNA vaccines	S protein	No	No infectious virus needs to be handled, easy scale up, low production costs, high heat stability, tested in humans for SARS-CoV-1, rapid production	Vaccine needs specific delivery devices to reach good immunogenicity.
Recombinant protein vaccines	S protein	Yes for baculovirus (influenza, HPV) and yeast expression (HBV, HPV)	No infectious virus needs to be handled, adjuvants can be used to increase immunogenicity	Global production capacity might be limited. Antigen and/or epitope integrity needs to be confirmed. Yields need to be high enough.
Viral vector-based vaccines	S protein	Yes for VSV (Ervebo), but not for other viral vectored vaccines	No infectious virus needs to be handled, excellent preclinical and clinical data for many emerging viruses, including MERS-CoV	Vector immunity might negatively affect vaccine effectiveness (depending on the vector chosen)
Live attenuated vaccines	Whole virion	Yes	Straightforward process used for several licensed human vaccines, existing infrastructure can be used	Creating infectious clones for attenuated coronavirus vaccine seeds takes time because of large genome size. Safety testing will need to be extensive
Inactivated vaccines	Whole virion	Yes	Straightforward process used for several licensed human vaccines, existing infrastructure can be used, has been tested in humans for SARS-CoV-1, adjuvants can be used to increase immunogenicity	Large amounts of infectious virus need to be handled (Could be mitigated by using an attenuated seed virus). Antigen and/or epitope integrity needs to be confirmed

Human coronaviruses and antibody-dependent enhancement (ADE)

The immunopathological effects of antibody-dependent enhancement (ADE) have been observed in various viral infections, characterized as antibody-mediated enhancement of viral entry and infection of a severe inflammatory response.^{332,333} ADE of viral entry has been observed for many viruses. It was assumed that antibodies target one serotype of viruses but only subneutralize another, leading to ADE of the latter viruses. This phenomenon has been reported *in vitro* and *in vivo* for viruses representing numerous families and genera of public health and veterinary importance, which share some common features such as preferential replication in macrophages, ability to establish persistence, and antigenic diversity. For SARS-CoV, it was suggested that antibodies against spike proteins of SARS may cause ADE effect which raised reasonable concern regarding the use of SARS-CoV vaccine and shed light on some roles in SARS pathogenesis. There are conflicting data for the role of ADE in serious coronavirus infections. Antibodies against the S protein can enhance virus uptake by cells *in vitro*, although the clinical relevance of these findings is conflicting. It has been reported that the rush to make a vaccine for SARS-CoV-2 may lead the infections worse, because the main risk is the chance of inducing ADE, a process known to complicate vaccine development which has happened before in Dengue and several other diseases. For previous human coronaviruses, SARS and MERS, antibodies against the viruses have been shown to cause ADE in animal models, including non-human primates, and like those viruses, it is important to be aware of the possibility of ADE caused by SARS-CoV-2 vaccines. ADE allows the infection of phagocytic antigen-presenting (APC), such as macrophages, due to the binding of virus-bound antibodies to FcγR on their surface.³³³ It has been shown that neutralizing antibodies

targeting the receptor-binding domains (RBD) of the MERS-CoV and SARS-CoV spike proteins, respectively, can mediate the entry of the viruses into Fc receptor-expressing human cell *in vitro*.³³⁴ Furthermore, T cells, believed to play an important role in controlling SARS-CoV-2 infection, are depleted in severe SARS-CoV-2,³³⁵ and this may be accelerated APC infection due to ADE.³³⁶ Recently, scientists have reported that unlike in MERS and SARS, the S-protein RBD of SARS-CoV-2 can elicit a robust neutralizing antibody response without including ADE in animal immunization studies.³³⁷

The majority of SARS-CoV-2 vaccines in development aim to elicit neutralizing antibodies against the spike protein that prevent the virus from binding ACE2 on lung cells and entering via endocytosis. Immunofocusing constitutes one of the main methods proposed to prevent ADE and skew adaptive immunity toward protective responses, and other immunofocusing strategies consist of making undesired antibody epitopes with glycosyl groups; truncating the spike protein, and locking the antigen into conformations which display epitopes for neutralizing antibodies.

On the basis of small cohorts of SARS-CoV-2 patients, two studies have shown that an increased IgG response and a higher titer of total antibodies were associated with more severe disease,^{338,339} which suggestive of possible ADE in SARS-CoV-2 infection,³⁴⁰ but there are still some doubts over the relevance of ADE in SARS-CoV-2. In some clinical studies, it has been revealed that SARS-CoV-specific antibodies are not harmful in patients with SARS, although it has been noted that non-neutralizing coronavirus antibodies may cause ADE in feline infectious peritonitis. Such efforts have promoted investigators to remove potential ADE-promoting S protein epitopes located outside the RBD and focus on the RBD as a lead vaccine candidate.^{341,342} There is no evidence that ADE facilitates the spread of SARS-CoV in infected

Table 22. Translational considerations for SARS-CoV-2 vaccine development.³⁵⁰

Stage	Translational category	Activity
T0	Basic Research	Characterize antibody-dependent enhancement (ADE) mechanisms Identify SARS-CoV-2 ADE-associated epitopes Bioinformatics of SARS-CoV-2 mutations Generating recombinant vaccine proteins Animal models for SARS-CoV-2 vaccines Phase 1 clinical trials
T1	Preclinical Research	Assay development for human anti-SARS-CoV-2 IgG Assay development for neutralizing versus ADE-inducing human IgG Assess effects of vaccine on ADE induction in animal models Modify vaccines to minimize ADE risk Phase 2/3 clinical trials Consider limiting initial vaccine studies to subjects ≥ 20 years old Multiplex measurement of anti-COVID IgG Outcomes research Phase 4 clinical trials
T2	Clinical Research	
T3	Clinical Implementation	Long-term follow-up of post-vaccinated and infected subjects for ADE Reexamine age indications for SARS-CoV-2 vaccination
T4	Public Health	Population-level studies of vaccine efficacy Assessment of ADE-associated antibody prevalence

hosts; in fact, infection of macrophages through ADE does not result in productive viral replication and shedding.³⁴³ Instead, internalization of virus-antibody immune complexes can promote inflammation and tissue injury by activating myeloid cells via FcRs.³⁴⁴ Virus introduced into the endosome through this pathway will likely engage the RNA-sensing Toll-like receptors (TLRs) TLR3, TLR7, and TLR8. Uptake of SARS-CoV through ADE in macrophages led to elevated production of TNF and IL-6. In mice infected with SARS-CoV, ADE was associated with decreased levels of the anti-inflammatory cytokines IL-10 and TGF β and increased levels of the proinflammatory chemokines CCL2 and CCL3.³⁴⁵ Recent studies of antibody responses in patients with SARS-CoV-2 have associated higher titers of anti-N IgM and IgG at all time points of following the onset of symptoms with a worse disease outcome.³⁴⁶ Furthermore, higher titers of anti-S and anti-N IgM and IgG correlated with worse clinical readouts and older age,³⁴⁷ suggesting potentially detrimental impacts of antibodies in some patients. But, 70% of patients who recovered from mild SARS-CoV-2 had measurable neutralizing antibodies that persisted upon revisit to the hospital.³⁴⁸

ADE should be given full consideration in the safety evaluation of emerging vaccines for SARS-CoV-2 and monoclonal antibodies could be used to tackle this virus.³⁴⁹ From studies about using a MERS-CoV vaccine, it has also been proposed that neutralizing antibodies might instead induce ADE. Vaccines are a routine medical intervention performed on healthy individuals, so it is important to consider ADE seriously during vaccine development to ensure that vaccines protect individuals and do not exacerbate disease following subsequent infections. Translational considerations for SARS-CoV-2 vaccine development, and vaccine platforms for human coronaviruses are presented in Tables 22 and 23, respectively.

Conclusion

Severe acute respiratory syndrome (SARS) is caused by a coronavirus SARS-CoV which was started in pigs or ducks in south of China and mutated to affect humans. It was originated in Guangdong province. CoVs are single-stranded RNA viruses which belong to the order Nidovirales, family Coronaviridae, and subfamily Coronavirinae. SARS is caused by a coronavirus (SARS-CoV) which exists in bats and palm civets in Southern China. Its family is *Coronaviridae*, and its genus is *Coronavirus*. It is enveloped, helical nucleocapsid, spherical to pleomorphic, helical nucleocapsid, spherical to pleomorphic, kidney-shaped or rod-shaped particles, 100–130 nm in diameter. Its nucleic acid is linear, positive-sense, single-stranded RNA, ~29.8 kb in length. Virions sensitive to treatment with lipid solvents, nonionic detergents, formaldehyde, and oxidizing agents. The civet cat (palm civet) in Southeast Asia is likely source of introduction of the agent to humans. The SARS CoV RNA sequence found in palm civets is 99% identical to that found in palm civets is 99% identical to that found in humans. Similar RNA sequences have been found in bats, snakes and monkeys. No medication has been proven to treat SARS effectively, but oxygen therapy and tracheal intubation and mechanical ventilation to support life until recovery begins is useful for patients in severe case. The most useful ways to control SARS pandemic is public-health and infection-control measures. The most important primary measures are isolation, ribavirin, and corticosteroid therapy, mechanical ventilation, convalescent plasma, and others. It can be spread from close person-to-person contact via respiratory droplets which come in contact with skin or mucous membranes such as eyes, mouth or nose.

MERS-CoV is a zoonotic virus which can lead to secondary human infections. Dromedary camels have been recognized as the intermediate host, with closely related virus sequences in bats. MERS carries a 35% mortality rate. There is no clear and specific treatment for MERS, and person to person spread causes hospital and household outbreaks of MERS-CoV. It is the sixth coronavirus that influences human. Like other coronaviruses, it is an enveloped single-stranded RNA virus which replicates in the host-cell cytoplasm, with approximate size of 30 kb. It has structural proteins, called the E, M, and N proteins, and membrane protein called the spike (S) protein, which has important role in the virus attachment and entry into the host cells. It has been concluded that the MERS-S protein is known to represent a key target for the development of new therapeutics and includes of a receptor-binding subunit S1 and a membrane-fusion subunit S2. The subunit S1 is composed of four different core domain, and the domain S1B binds to the host-cell receptor dipeptidylpeptidase 4 (DPP4), while the domain S1A binds to sialoglycans which increased infection of human lung cells by MERS-CoV. The roles of S protein in receptor binding and membrane fusion make it a perfect target for vaccine and antiviral development. It has been showed that vaccines based on the S protein can induce antibodies to block virus binding and fusion or neutralize virus infection.

The novel SARS-CoV-2, which apparently first infected people in the city of Wuhan, spread in all over the world. Its genome sequence analysis has shown that SARS-CoV-2 belongs to beta-coronavirus genus, which includes Bat SARS-like coronavirus, SARS-CoV and MERS-CoV. On the basis of nucleic acid

Table 23. Vaccine platforms for Human coronaviruses.

	Target	MERS-CoV	Target	SARS-CoV-2	Target
Inactivated SARS virus (β-propiolactone, formalin, UV, irradiation)	All virus structural proteins	Live attenuated MERS-CoV (E envelope-deleted)	All virus genome component s (except E)	Inactivated virus/alum	All structural proteins of the virus
Live attenuated/host adapted SARS virus (E-deleted)	All genome (except the envelope protein)	Chemically for physically-inactivated virus (MERS-CoV, rabies virus)	S glycoprotein and S1 subunit	Virus-like particle (VLP)	Unknown
Live attenuated recombinant virus (parainfluenza virus, Vesicular Stomatitis Virus, Venezuelan equine encephalitis virus, Newcastle disease virus)	S glycoprotein Nucleocapsid (N) protein	Replication-deficient viral-vectored vaccines (Poxvirus, adenovirus, measles, rabies)	S glycoprotein or S1 subdomain (containing the receptor-binding protein)	Protein nanoparticles/Matrix-M	S glycoprotein
Recombinant modified vaccinia Ankara (MVA) virus	Spike (S) glycoprotein or nucleocapsid (N) protein	Soluble protein vaccines/adjuvant	S glycoprotein and fragments	Non-replicating viral vector (adenovirus, chimeric chimpanzee adenovirus)	S glycoprotein/unknown
Recombinant non-replicating adenovirus (E-deleted)	S glycoprotein/nucleocapsid (N) protein	Nanoparticles	S glycoprotein	S glycoprotein/unknown	S glycoprotein/unknown
DNA-based vaccines	Full spike (S) glycoprotein of fragments	DNA-based vaccines	S glycoprotein and subunits	DNA-based vaccine	S glycoprotein/unknown
Soluble proteins/adjuvant	Full spike (S) glycoprotein of fragments	Combination vaccines (protein and DNA)	S glycoprotein and subunits	Protein subunit	S glycoprotein and peptides/unknown
Virus-like particles (VLPs)/adjuvant	Spike (S) glycoprotein			Live attenuated virus	All proteins of the virus
Combination of vaccine approaches (DNA/peptide, DNA/recombinant viral vector, viral vector/peptides)	S glycoprotein or fragments			Replicating viral vector (measles, horsepox)	Unknown

sequence similarity, the newly identified SARS-CoV-2 is a beta-coronavirus. The RBD portion of the SARS-CoV-2 spike proteins has evolved to effectively target a molecular feature on the outside of human cells called ACE2, a receptor involved in regulating blood pressure. The SARS-CoV-2 spike protein was found so effective at binding the human cells. In SARS-CoV-2, M protein is responsible for the transmembrane transport of nutrient, the bud release and the formation of envelope, S protein, attaching to host receptor ACE2, including two subunits S1 and S2. It has been reported that remdesivir only and in combination with chloroquine or interferon beta significantly blocked the SARS-CoV-2 replication and patients were declared as clinically recovered. Some other anti-virals like Nafamostat, Nitazoxanide, Ribavirin, Penciclovir, Favipiravir, Ritonavir, AAK1, Baricitinib, and Arbidol showed moderate results when tested against infection in patients and in-vitro clinical isolates. Isothermal nucleic acid amplification as a highly promising candidate method for detection of coronavirus infection, due to its fundamental advantage in quick procedure time at constant temperature without thermocycler operation.

Antibody dependent enhancement of viral infection is a process by which the virus leverages the antibodies to aid its infection. ADE allows the infection of phagocytic antigen-presenting cells (APC), such as macrophages, due to the binding of virus-bound antibodies to FcγR on their surface. Identification of viral epitopes associated with ADE neutralization is effective for development of vaccines with minimum or no risk for ADE. Also, clear understanding of the cellular events after virus entry through ADE has become crucial for developing efficient intervention, and it is necessary to better understanding the mechanisms of ADE.

The vaccine effort should be guided by three imperatives: speed, manufacture and deployment at scale, and global access. Once the vaccine found to be effective, it will be distributed to millions or billions of people. The amino acid sequences of the virus like in other viruses, might have a cross-reaction with the human body sequences. Researchers should work to develop effective and safe subunit vaccines against human coronaviruses, especially SARS-CoV-2 and any other emerging coronaviruses that might cause future pandemics.

Disclosure of potential conflicts of interest

The manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal. We have read and understood journal's policies, and we believe that neither the manuscript nor the study violates any of the rules. There are no conflicts of interest to declare.

Ethical approval

Not required.

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